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Relationship Between T2-Weighted Hyperintensities (Unidentified Bright Objects) and Lower IQs in Children With Neurofibromatosis-1

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To address the controversy regarding the relationship between cognitive impairment (lowering of IQ) and magnetic resonance imaging (MRI) characteristics (T2-weighted hyperintensities or unidentified bright objects [UBOs]) in children with neurofibromatosis-1 (NF-1), we used a pairwise NF-1/sibling design; we set out to predict the lowering of IQ in each child with NF-1 as a discrepancy from the IQ of an unaffected sibling (D-SIQ). Our multiple regression model included the age of the child with NF-1, familial or sporadic nature of the NF-1, number of locations in the child's brain occupied by T2-weighted hyperintensities (UBOs), and the volumetric percentage of brain tissue occupied by T2-weighted hyperintensities (UBOs). Only the number of locations occupied by UBOs accounted for IQ lowering (D-SIQ) in children with NF-1 (42% of the variance in D-SIQ). This is the first report to confirm that a continuum of lowered IQs in NF-1-affected children exists in relation to the distribution of UBOs (range 0–7), not just presence (vs. absence) of any UBOs.

KEY WORDS: NF-1, siblings, MRI, intelligence

INTRODUCTION

Neurofibromatosis type 1 (NF-1; Von Recklinghausen neurofibromatosis) is an autosomal dominant neurocutaneous syndrome with an incidence of approximately 1 : 4,000 among all ethnic groups. Central nervous system (CNS) involvement can be in the form of an optic pathway glioma or other glial tumor, a plexiform neurofibroma, dural ectasia, and occasionally aqueductal stenosis. In addition to these specific pathological lesions, cognitive impairment is common. Compared with an estimated 15% in the general population, the frequency of learning disabilities (LD) among NF-1 children ranges from 29% to 37% [Huson et al., 1988; Stine and Adams, 1989; Riccardi, 1992], and can be responsible for significant lifetime morbidity.

Using intracranial computed tomography (CT) imaging, it is possible to observe evidence of the optic nerve and parenchymal gliomas in individuals with NF-1. Since the advent of magnetic resonance imaging (MRI), high signal intensity foci on T2-weighted images (unidentified bright objects, or UBOs) have been noted. They are seen most frequently in the basal ganglia, cerebellum, brain stem, pons, midbrain, and internal capsule [Hofman et al., 1994; Itoh et al., 1994; North et al., 1994; Ferner et al., 1993]. Speculation as to UBO pathology include foci of abnormal myelination, hamartomas, heterotopias, and even low-grade tumors [Sevick et al., 1992]. Although considered by some to be pathognomonic [Duffner et al., 1989; Goldstein et al., 1989], they have yet to be incorporated among the criteria for the clinical diagnosis of NF-1 [Mulvihill, 1990]. The question of the frequency of these foci in an NF-1 population-based study has not been addressed, although they are relatively common among patients referred for MRI from NF-1 clinics, ranging from 53% to 79% [DiMario et al., 1993; Sevick et al., 1992; Itoh et al., 1994]. The foci appear to be age dependent, less often seen with advancing age [Aoki et al., 1989; Itoh et al., 1994]. In contrast to optic nerve or parenchymal gliomas, which may result in morbidity or mortality, the high signal intensity T2-weighted images (UBOs), at least based on relatively short-term follow-up [Sevick et al., 1992; Duffner et al., 1989], do not seem to progress to neoplastic lesions.

A correlation between cognitive impairment and the presence of glial and gray matter heterotopias at autopsy has long been suggested [Rosman and Pearce,

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1967]. In 2 studies which did not demonstrate any association between the presence/absence of UBOs and cognition [Dunn and Roos, 1989; Duffner et al., 1989], formal cognitive assessment was not performed on all the subjects. A more recent report that compares the IQs of children with NF-1 to general population IQ distribution indicates that children with UBOs are at risk for significantly impaired cognition [North et al., 1994]. NF-1-affected children who did not have UBOs demonstrated IQs close to the general population's mean IQ; those children with NF-1 and UBOs presented significantly lower mean full scale IQs (FSIQs) and a left (downward) distributional shift when compared to the general population.

Using a family-based, sibling-pair design in a previous study, we demonstrated that, compared to their unaffected siblings, children with NF-1 show a statistically significant correlation between the pairwise lowering of the FSIQ and the number of brain locations in which UBOs are seen ($P < 0.0003$) [Hofman et al., 1994]. In addition, other pairwise cognitive differences in neuropsychologic test scores correlated with the number of UBO-occupied sites.

The purpose of our current study was to contribute to the ongoing controversy regarding the association between T2-weighted intensities (UBOs) and cognitive deficits in NF-1. In order to take into account other familial factors (polygenic and environmental) that impact on cognition, the study was designed to compare an affected child with an unaffected sibling. The importance of using sibling IQ to set IQ expectancy is underscored by the fact that, in general, IQ tests of siblings reared together are more highly correlated (0.47) than is the IQ of any one child with the midparental IQ (Thompson and Petrill, 1994). In addition, since some (but not all) NF-1 children have a parent also affected by NF-1, using midparental IQ as that from which "lowering" is defined would introduce another source of variability in setting the "expectancy" for each NF-1 child's IQ. Comparing NF-1-affected children's IQs to those of the general population is only a first step in examining the possible role of MRI abnormalities in lowering these children's IQs. We take the process further by testing the hypothesis that the T2-weighted hyperintensities account for *lowering* an NF-1 child's IQ relative to what otherwise would have been expected for that child from that family.

Furthermore, we attempt to go beyond the study of North et al. [1994], who noted the dichotomous "presence or absence" of T2-weighted hyperintensities. We analyze a continuum of lowering of IQ as a function of 2 quantitative MRI findings: 1) percentage of brain tissue volume replaced by abnormal signal and 2) the number of brain locations occupied by these abnormalities.

MATERIALS AND METHODS

Population and Procedure

Twenty sibling pairs (each consisting of an NF-1-affected child aged 6–14 years and an unaffected sibling aged 7–17 years) and their parents completed the research protocol consisting of an MRI and, within the same week, testing (psychoeducational, speech/language, and neuropsychological). All children were free of seizures and brain tumors and met the criteria specified in a previous publication describing the first 12 sibling pairs and their families [Hofman et al., 1994]. This report is concerned with IQ measures only; thus only IQ measures are herein described. See prior publication [Hofman et al., 1994] for more detail regarding test protocol. The Wechsler Intelligence Scale for Children-Revised (WISC-R) was used as the IQ test for children. Parents were tested for IQ using 4 subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) that yield an estimated FSIQ, shown to correlate (0.9) with complete WAIS-R [Silverstein, 1982]. Scheduling for convenience, they were tested simultaneously with their children.

By closely examining descriptive data, it was noted that one unaffected sibling of a child with sporadic NF-1 was an outlier, being the only unaffected sibling whose FSIQ was more than 5 points lower than his NF-1-affected sibling (it was 22 points lower) and whose discrepancy from midparental IQ (D-MPIQ) was greater than 7 points (it was 21 points lower); by contrast, the mean D-MPIQ for unaffected siblings was -3, SD 10. Another diagnosis (other than NF-1) was found to be a possible cause for the lower IQ of this unaffected sibling of a sporadic NF-1 subject. Therefore, this sibling pair and parents were omitted from the remainder of analyses.

MRI Acquisition

All subjects had MRI scans with a 1.5-T Signa MR scanner (General Electric, Milwaukee, WI). A T1-weighted sagittal series (TR = 600, TE = 20) was obtained first for identification of the anterior and posterior commissure (AC-PC line). Three axial series were obtained parallel to the AC-PC line: a double echo (spin density/T2-weighted) sequence (TR = 3,000, TE = 30, 100), a T1-weighted sequence (TR = 500–600, TE = 20), and a magnitude inversion recovery sequence (TR = 3,000, TE = 20, TI = 500). The spin density, T2, and T1 axial sections were obtained with 5 mm thick, contiguous slices and a field view of 22–24 cm. The inversion recovery images were obtained from the level of the fourth ventricle to above the corpus callosum, with 3 mm thick contiguous slices and a field view of 20 cm. Up to 10 locations could be scored as positive for increased signal intensity: right and left sides of the basal ganglia, brainstem, cerebrum, cerebellum, and deep nuclei.

MRI Post-Acquisition Processing and Volumetric Analysis of UBOs

Analysis of NF-1 lesions was based on the T2-weighted images, regions of abnormally increased T2-weighted signal intensity greater than normal gray matter but no mass effect. Quantitative volumetric measurements were performed on an ISG Digital Image Workstation. Lesions were initially defined by visual inspection of the slices by the reader, digitally defined as regions of interest (ROIs) by manually thresholding the raw images to exclude normal brain

and cerebrospinal fluid (CSF), leaving only the bright lesions visible. For each slice, a seed-based segmentation algorithm was initiated by placing a "seed" in the center of each lesion. The algorithm then automatically flooded the similar, contiguous region using a local histogram analysis and an edge detection protocol. The algorithm then attempted to automatically drop a seed into similar regions on adjacent slices and perform the same lesion segmentation operation, while allowing *adjustment* of the final ROI by the operator. After the lesion ROIs were performed on each slice, a volume of interest (VOI) of each lesion was reconstructed from the segmented slices by linear interpolation of the original multislice, 2D dataset into a 512 × 512 × 512 dataset. Each VOI was calculated in millimeters and 12 VOIs in the same dataset were simultaneously managed. Further details describing these procedures are described in Herman [1992].

For NF-1 lesion identification, the semi-automatic tissue segmentation algorithm of the ISG workstation was considered only as an operator aid, since the final VOI determination was confirmed by the reader's eyes. There was no disagreement between 2 neuroradiologists who separately analyzed each case for lesion identification. Lesion volumes were calculated by the first reader and visually confirmed by the second reader.

Processing and Segmentation of Double-Echo, Spin Density Scans for Volumetric Analysis of Brain Tissue and CSF

This procedure was primarily based on methods described by Lim and Pfefferbaum [1989]. CSF and brain tissue measures are described in detail elsewhere [Reiss et al., 1993, 1995]. Skull and nonbrain tissues were removed from paired double echo images using an automated edge detection algorithm. Composite images were then made by summing the paired double echo images (producing accentuated gray-white contrast) or subtracting the early from the late echo image (producing accentuated tissue-CSF contrast). Shading artifact caused by radiofrequency field inhomogeneity was then removed from these composite images through a series of filtering steps. Determination of tissue and CSF volumes in each slice used an automated segmentation procedure that designates each voxel as belonging to a particular tissue class and then sums the designated voxels from each slice. Because scans obtained from double echo acquisition did not extend artifact free from vertex to foramen magnum in all subjects, CSF and brain tissue measures were obtained from a representative volume which extended from the inferior slice marking the medullary-pontine junction to a superior slice containing the top of the body of the lateral ventricles.

Statistical Plan and Analysis

The data set consisted of 1) WISC-R-derived FSIQ for 20 pairs of children (NF-1 and sibling of NF-1); 2) WAIS-R (short form)-derived IQ for each parent; 3) a "lesion count" for number of locations in which UBOs were seen (NF-1 children only); and 4) a UBO/brain ratio, i.e., total summed volume of UBOs (lesions) divided by total brain tissue volume. Furthermore, whether each child had a parent with NF-1 was noted, i.e., familial vs. sporadic status, and coded as NF-1 parent "yes"/"no."

Derived from the dataset were midparental IQ and "discrepancy IQs" of 2 types: 1) child from midparental (D-MPIQ) and 2) NF-1-affected child from unaffected sibling (D-SIQ).

For NF-1 children, multiple regression was the main analysis, using as a dependent variable the discrepancy from sibling IQ (D-SIQ) and using as independent variables the number of brain regions occupied by UBOs, the ratio of total UBO volume to total brain tissue volume, age, and familiality status. Descriptive statistics, Spearman rank correlations, and simple regression plots were also calculated.

RESULTS

See Table I for the characteristics of the 19 pairs (7 familial and 12 sporadic) included in the analysis.

Regression procedures were carried out to examine which of several independent VOIs most strongly predicted intellectual outcome in children with NF-1. The dependent variable was the lowering of the NF-1-affected child's IQ relative to that of the child's unaffected sibling, as described earlier (D-SIQ). Of primary interest was whether the number of UBO locations and the summed volume of UBO tissue (total UBOs/total brain tissue ratio) were associated with the D-SIQ scores.

The results of 2 simple regression analyses revealed that total UBO volume was not associated with D-SIQ, $F = 2.88$; and that the number of UBO locations did account for a significant portion (42%) of the variance in D-SIQ, $F\ (1, 17) = 12.110$, $P = .0029$. Although these 2 UBO measures were positively correlated, Spearman $Rho = .82$, $P < .001$, only the latter was significantly associated with D-SIQ.

Of interest was whether the inclusion of variables in addition to number of UBO locations would strengthen the regression model. The addition of child's age at MRI scan, familiality (whether the NF-1 child has a parent who has NF-1), or summed UBO volume did not significantly strengthen the regression model based on number of UBO locations, as seen in Table II.

See Table III for distribution of UBO-occupied locations in 19 children with NF-1.

The mean D-SIQ for the NF-1-affected children was 13 points (SD ± 8.9 points). The mean number of UBO-occupied locations (NF-1 children only) was 3 (SD ± 2), with basal ganglia the minimal and therefore most frequent site. The range was 0–7 UBO-occupied locations.

TABLE I Ages and IQ's of Subjects

	Age		FSIQ		MPIQ[a]	
Group	M	(SD)	M	(SD)	M	(SD)
NF-1 (n = 19)	9.9	(2.4)	94.8	(11.4)	104.0	(10.6)
Siblings (n = 19)	10.1	(2.5)	108.3	(11.2)	104.0	(10.6)

[a] Same for NF-1 group and their unaffected siblings as these are paired.

TABLE II. Results of Different Regression Models with D-SIQ as the Dependent Variable

Independent variables	F value	*P* value
Number of locations	12.110	.0029
UBO volume/total brain tissue volume ratio	2.88	.1078
Number of locations + age	7.967	.0040
Number of locations + familiality	5.734	.0133
Number of locations + UBO volume	5.753	.0131
Number of locations + UBO volume + age	6.031	.0066
Number of locations + familiality + age	5.029	.0131
Number of locations + UBO volume + familiality	3.614	.0382
Number of locations + UBO volume + age + familiality	3.585	.0326

The 3 pairs of siblings in whom zero UBOs were seen in the NF-affected child included the only reversed D-SIQ (NF-1 child's IQ higher than that of sibling) and 2 of the 4 pairs in the group (n = 19) whose IQs were within 5 IQ points of each other's IQ.

DISCUSSION

These data are convergent with the conclusions of North et al. [1994] in that they confirm the relevance to the "left shift" in IQ in children with NF-1 of T2-weighted hyperintensities (UBOs). Because ours was a family-based study, enabling us to address lowering of IQ in children with NF-1 in relation to that of their own unaffected siblings, we have avoided the potential sampling bias implicit in comparing children with NF-1 to general population norms [North et al., 1994]. Our study allows us to compare the IQs of individuals with NF-1 to what might otherwise have been expected of them. This was exemplified in our study by several families whose unaffected members were of superior IQ; lowered by NF-1 into the average range, the affected child's IQ did not differ from the general population's mean IQ. Furthermore, unlike all previous studies addressing IQ and T2-weighted hyperintensities, this study moves beyond the dichotomy, "UBO+/UBO−"; we examined both number of UBO-occupied locations and percentage of brain tissue volume occupied by UBOs as separate continuously distributed anatomic deviations that might predict IQ-lowering in children with NF-1.

Additionally, we excluded the optic pathway UBOs that coexisted with those in other locations in 64% of all UBO-positive cases reported by North et al. [1994]; we did so because of the greater likelihood that optic pathway hyperintensities might represent tumors (gliomas) and/or might have visual-functional significance. Thus, in our study the UBOs represent the more subtle and benign (less tumor-suspect) range of MRI-apparent "lesions" characteristic of NF-1, yet the number of places in the brain occupied by such "lesions" did predict, as in our earlier report involving 12 sibling pairs, sibling-referenced lowering of IQ. Sporadic or familial NF-1 status did not influence this prediction. Volumetric analysis failed to add to the predictive power afforded by knowing the number of places where pathways in the brain are presumably interrupted by the UBOs.

It may seem surprising that the percentage volume of brain tissue occupied by UBOs failed to show an independent impact upon IQ. It is to be noted, however, that in the 16 cases in whom UBOs were seen, the range of percentages was 0.1–7.7%, which does not represent a large mass effect. In any event, IQ itself, as a broad-band or composite index of cognition, might reasonably be more adversely affected by multiple interruptions in CNS connections than by volume replacement in one or more specific locations. Any one location's volumetric "lesion" might have an impact on some specific cognitive capacity heavily dependent on that structure. Some pilot data exist to the effect that total volume of UBOs within the most commonly occupied site, the basal ganglia, does indeed adversely affect scores on the test most commonly impaired in many studies of NF-1, namely, Judgment of Line Orientation Test [Mott et al., 1994]. The theme that cognitive deficits in NF-1, both for IQ and for more specific aptitudes, are attributable to largely subcortical pathway "lesions" is one that merits emphasis. Major roles are implied for basal ganglia and cerebellum and/or pathways interconnecting these with the cortex [Middleton and Strick, 1994].

The nature of the "lesions" called UBOs remains controversial; as reviewed in more detail by others [Sevick et al., 1992; Ferner et al., 1993; Zimmerman et al., 1992] the increased T2 signal intensity has been thought to represent dysmyelination, hamartomas, heterotopias, or even edema. Although seen in the majority of children with NF-1, the UBOs are rarely seen in older adolescents or adults [Aoki et al., 1989; Itoh et al., 1994]. An intriguing fact to set alongside the age-related lower prevalence of UBOs is the observation of more average (less left or down-shifted) IQs in adults with NF-1 [Riccardi, 1992]. It is unknown whether the disappearance of hyperintense signal on MRI indicates

TABLE III. Locations of UBOs per NF-1 Subject

3	No UBOs
2	Basal ganglia only
5	Basal ganglia and brainstem
2	Basal ganglia and cerebral peduncle
2	Basal ganglia and cerebellum
1	Basal ganglia, brainstem, and subcortical
2	Basal ganglia, brainstem, and cerebellum
1	Basal ganglia, brainstem, cerebellum, and subcortical
2	Basal ganglia, brainstem, cerebellum, and other[a]

[a] One thalamus, one claustrum.

equally significant improvements in the microscopic organization and myelination of underlying brain tissue. If cognition improves with maturation, this may be by means of compensatory strategies, rather than because the dysplastic or dysmyelinated brain has normalized. Disappearance of T2-weighted hyperintense signals may, alternatively, herald the normalization of underlying brain; but it is possible, from the perspective of "critical period theory," to predict that normalization of anatomic structure may come too late to allow for fully realized cognitive capacities to emerge. We have begun a longitudinal study of some of the families whose initial data have been included in this report; repeating MRIs and measuring cognition in reference to that of unaffected siblings will, with multiple points, allow for individual cognitive growth curve analyses to be correlated with the fate of UBOs. Also planned is examination in a sibling pair design of the contribution to cognitive deficits of regional macrocephaly in NF-1, although overall macrocephaly has not emerged as a contributor to IQ [Rubinstein, 1986], since enlargement of the volume of certain brain structures may be an indicator of anomalous maldevelopment [Reiss et al., 1994].

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